Inconsistent Labeling of Food Effect for Oral Agents across Therapeutic Areas: Differences between Oncology and Non-Oncology Products

Soonmo Peter Kang¹,² and Mark J. Ratain¹,²,³

Abstract

Purpose: Several recent oral oncology drugs were labeled for administration in fasted states despite the fact that food increases their bioavailability. Because this was inconsistent with the principles of oral drug delivery, we hypothesized that there were inconsistencies across therapeutic areas.

Experimental Design: Oral agents approved by the U.S. Food and Drug Administration from January 2000 to May 2009 were included in our study. Comparison of the food labeling patterns between oncology and non-oncology drugs was made using Fisher’s exact test.

Results: Of the 99 drugs evaluated, 34 showed significant food effects on bioavailability. When food markedly enhanced bioavailability, eight out of nine non-oncology drugs were labeled “fed” to take advantage of the food-drug interaction, whereas all oncology drugs (n = 3) were labeled to be administered in “fasted” states (Fisher’s exact test, P = 0.01).

Conclusions: Drug labeling patterns with respect to food-drug interactions observed with oncology drugs are in contradiction with fundamental pharmacologic principles, as exemplified in the labeling of non-oncology drugs. Clin Cancer Res; 16(17); 4446–51. ©2010 AACR.

Materials and Methods

The present study is based on the examination of all new molecular entities (NME) that were approved for oral administration by the U.S. Food and Drug Administration (FDA) between January 2000 and May 2009. The primary source of data was the FDA web site (http://www.accessdata.fda.gov/scripts/cder/drugsatfda). This included both clinical pharmacology/biopharmaceutics reviews and labels. A search of published literature was conducted in PubMed (http://www.ncbi.nlm.nih.gov/pubmed) to gather missing information from the FDA web site (7–19). Main search terms used were food effect, bioavailability, pharmacokinetics, and the agents’ names.

Data captured for the purpose of the present analysis included drug approval date, drug name, therapeutic area, magnitude of food effect, interindividual variability (IIV)
of area under the curve (AUC) of fed and fasted states, dosing recommendation with regards to meals (fed, fasted, or either), and black box safety warnings in drug labels.

We included all NMEs with food effect bioavailability study results available on the FDA web site or via publication, and divided them into two categories (oncology versus non-oncology) based on their indications and divisions of the U.S. FDA involved in the approval processes. We used AUC as the reflection of the extent of drug exposure, and used the ratio of fed to fasted AUC to measure the food effect. In keeping with guidance from the FDA, food effect was determined to be significant if the AUC ratio (fed/fasted) was >1.25 or <0.8 (20). We then subclassified NMEs with a ratio >1.5 and <0.5, a magnitude of food effects that will likely have clinical implications. A comparison of food effects was made between oncology and non-oncology drugs that met these criteria.

The dosing recommendations regarding meal intakes (fasted, fed, or either) available in the dosage and administration section of package inserts were surveyed to study how food effect results are applied. Comparison of the drug label patterns between oncology and non-oncology drugs with marked food effects were made by using Fisher’s exact test. To assess the effect of food intake on IIV of AUC, we compared coefficients of variation (CV) of AUC between fasted and fed states of 23 drugs with significant food effects and available PK data. Black box safety warnings were available from package inserts and the frequency of black box warnings were compared between oncology and non-oncology drugs. We also surveyed package inserts of NMEs...
with black box warnings to identify warnings related to food intake and associated risks.

**Results**

We identified 104 oral NMEs that were approved by the FDA between January 2000 and May 2009. This included 11 oncology drugs and 93 non-oncology drugs. Most of these NMEs (n = 99) had food effect study results reported in the clinical pharmacology section of the package inserts.

**Influence of meals on drug exposure**

Of 99 NMEs with available food effect study results, about one-third (n = 34) showed significant food effects on their bioavailability. Marked food effects were observed in nearly 20% of drugs (14 increasing and 4 decreasing AUC). Of the 18 NMEs with marked food effects, 3 were oncology agents and 15 were non-oncology agents.

**Application of food effect study to drug labeling**

The vast majority (94%, n = 93) of NMEs had specific recommendations with respect to food coadministration: 60% (n = 56) without regard to meals, 24% (n = 22) to be administered with food, and 16% (n = 15) to be administered in the fasted state. Only six NMEs had no specific recommendations regarding food intake.

Analysis of 14 NMEs with marked increase in AUC with food revealed that there are different food labeling patterns between oncology and non-oncology drugs. For the non-oncology drugs, the marked increase in bioavailability with food generally (with one exception) led to recommendations to administer drugs in a fed state to take advantage of the favorable food effects. The opposite labeling pattern was observed for oncology drugs, as all three drugs with a marked increase in bioavailability with food were recommended to be administered in fasting states (Fig. 1).

Food significantly decreased (by ≥20%) the bioavailability of 11 NMEs, and the majority were labeled to be administered in fasted state (7 fasted, 1 fed, and 3 either). Sorafenib was the only oncology NME in this group, which is labeled to be taken fasting. Four NMEs showed a marked decrease of bioavailability (by ≥50%) with food, and all of them were labeled to be administered in a fasted state to maximize their bioavailability (Fig. 1).

**Influence of meals on IIV of AUC**

Of 34 NMEs with significant food effects, 23 had CV data available through the FDA web site (package insert or Clinical Pharmacology and Biopharmaceutics Review)

### Table 1. Summary of food effects and labels of 23 NMEs that were approved by the FDA from January 2000 to May 2009

<table>
<thead>
<tr>
<th>Name</th>
<th>AUC ratio (fed/fasted)</th>
<th>CV fasted</th>
<th>CV fed</th>
<th>CV fed-CV fasted</th>
<th>Label</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lapatinib</td>
<td>4.1</td>
<td>68%</td>
<td>52%</td>
<td>−16%</td>
<td>Fasted</td>
</tr>
<tr>
<td>Posaconazole</td>
<td>3.6</td>
<td>36%</td>
<td>41%</td>
<td>5%</td>
<td>Fed</td>
</tr>
<tr>
<td>Erlotinib</td>
<td>2.09</td>
<td>36%</td>
<td>18%</td>
<td>−18%</td>
<td>Fasted</td>
</tr>
<tr>
<td>Alfuozisin HCl</td>
<td>2</td>
<td>69%</td>
<td>40%</td>
<td>−29%</td>
<td>Fed</td>
</tr>
<tr>
<td>Ziprasidine HCl</td>
<td>2</td>
<td>44%</td>
<td>22%</td>
<td>−22%</td>
<td>Fed</td>
</tr>
<tr>
<td>Nitazoxanide</td>
<td>1.9</td>
<td>35%</td>
<td>37%</td>
<td>2%</td>
<td>Fed</td>
</tr>
<tr>
<td>Rifaximin</td>
<td>1.89</td>
<td>51%</td>
<td>26%</td>
<td>−25%</td>
<td>Either</td>
</tr>
<tr>
<td>Nilotinib</td>
<td>1.74</td>
<td>35%</td>
<td>30%</td>
<td>−5%</td>
<td>Fasted</td>
</tr>
<tr>
<td>Cinacalcet</td>
<td>1.68</td>
<td>60%</td>
<td>46%</td>
<td>−14%</td>
<td>Fed</td>
</tr>
<tr>
<td>Deferasirox</td>
<td>1.62</td>
<td>36%</td>
<td>31%</td>
<td>−5%</td>
<td>Fasted</td>
</tr>
<tr>
<td>Etravirine</td>
<td>1.54</td>
<td>111%</td>
<td>80%</td>
<td>−31%</td>
<td>Fed</td>
</tr>
<tr>
<td>Vorinostat</td>
<td>1.38</td>
<td>43%</td>
<td>32%</td>
<td>−11%</td>
<td>Fed</td>
</tr>
<tr>
<td>Rufinamide</td>
<td>1.34</td>
<td>30%</td>
<td>28%</td>
<td>−2%</td>
<td>Fed</td>
</tr>
<tr>
<td>Gefitinib</td>
<td>1.33</td>
<td>55%</td>
<td>40%</td>
<td>−15%</td>
<td>Either</td>
</tr>
<tr>
<td>Darunavir</td>
<td>1.3</td>
<td>15-35%</td>
<td>15-35%</td>
<td>0%</td>
<td>Fed</td>
</tr>
<tr>
<td>Tapentadol</td>
<td>1.26</td>
<td>36%</td>
<td>29%</td>
<td>−7%</td>
<td>Either</td>
</tr>
<tr>
<td>Rasagiline</td>
<td>0.8</td>
<td>30%</td>
<td>32%</td>
<td>2%</td>
<td>Either</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>0.76</td>
<td>125%</td>
<td>150%</td>
<td>25%</td>
<td>Fasted</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>0.69</td>
<td>36%</td>
<td>53%</td>
<td>17%</td>
<td>Fasted</td>
</tr>
<tr>
<td>Sodium oxybate</td>
<td>0.65</td>
<td>38%</td>
<td>42%</td>
<td>4%</td>
<td>Fasted</td>
</tr>
<tr>
<td>Tegaserod maleate</td>
<td>0.42</td>
<td>26%</td>
<td>32%</td>
<td>6%</td>
<td>Fasted</td>
</tr>
<tr>
<td>Ertomobopag</td>
<td>0.41</td>
<td>28%</td>
<td>27%</td>
<td>−1%</td>
<td>Fasted</td>
</tr>
<tr>
<td>Aliskiren</td>
<td>0.3</td>
<td>49%</td>
<td>60%</td>
<td>11%</td>
<td>Fasted</td>
</tr>
</tbody>
</table>

NOTE: NMEs with both AUC and CV data available were included.
or via publications (Table 1). In general, we observed an inverse relationship between food effects on bioavailability and IIV. In most cases, increase of bioavailability with food resulted in a decrease of IIV of AUC (Fig. 2). Of 16 drugs with a significant increase of bioavailability with meals (and with available CV data), only one drug (posaconazole) showed an increase of bioavailability associated with a slight increase of IIV; the CV increase with food was merely 5%. The CVs of three oncology drugs with marked positive food effects were decreased by food intake, which indicate that coadministration of drugs with food did not add to the risk of unpredictable exposure, but in fact improved the exposure variability probably as a result of enhanced bioavailability. On the other hand, when food had a negative effect on a drug’s bioavailability, administering the drug with food resulted in greater IIV compared with administering it without food (Fig. 2).

Safety warning label
We surveyed NMEs with a black box safety warning to determine whether marked food-drug interactions are incorporated in such a warning. The frequencies of black box warnings were similar between oncology and non-oncology drugs (36% versus 32%). Of three drugs with marked food-drug interactions, only one NME (nilotinib) had its food effect on drug exposure clearly described in the black box safety warning. Lapatinib, which showed the greatest food effect on its AUC, did not have a black box warning regarding its food-drug interaction, even though QT prolongation is an acknowledged risk (Table 2).

Discussion
Dosing strategies to enhance bioavailability offer several advantages to delivery of oral drugs. They include reduced gastrointestinal toxicity (from unabsorbed drugs) and decreased intraindividual and/or IIV in drug exposure (4, 21). Increased drug absorption also reduces wasted drug product and improves pharmacoeconomic efficiency.

Unwarranted food restrictions might compromise the practicality of drug administration for patients and result in decreased adherence. The complexity of the drug regimen is a major reason for nonadherence, and interventions such as reminder systems have been shown to improve adherence (3, 22–26). Daily routines such as breakfast, could serve as great reminders to take medications consistently. Hence, a dosing schedule tied to routine meals will be easier for patients (particularly elderly cancer patients taking multiple oral medications) and can be a great way to improve adherence, which is recognized as a serious challenge in cancer treatments with oral agents.

Fig. 2. Relationship between food effects on bioavailability and interindividual variation of drug exposure. Y-axis represents change in coefficient of variance of AUC from fasted to fed states. X-axis represents food effect on mean AUC. Examination of 23 drugs with significant food effects and available CV data revealed an inverse relationship between change in BA and change in IIV of drug exposure from prandial states.
The food labeling pattern of recently approved oral oncology drug products is inconsistent with fundamental principles of oral drug delivery. The labels of three agents (erlotinib, nilotinib, and lapatinib) minimized bioavailability through food restrictions, which is in contrast to the labeling principles used for all other classes of oral agents. In the absence of a scientific basis for food restrictions, one can hypothesize that the atypical food labeling pattern of some oral oncology drug products might be a consequence of external pressures (corporate and regulatory pressures) in an era of immense competition in oncology. Phase II (and occasionally registration) studies are often initiated prior to the completion of an appropriate food-effect study (14, 27). Because the default position seems to be fasting, this has occasionally resulted in the completion of all clinical studies with a fasting dosing regimen in the absence of adequate supportive pharmacokinetic data (14, 27, 28). Furthermore, there is little interest from the industry in conducting such studies later if the result would be a lower labeled dose because this would result in reduced revenues, unless accompanied by an increase in pricing. Thus, regulators should require such studies after approval, if the prior studies have not adequately addressed this issue.

A food effect study conducted in a timely fashion could facilitate pharmacologically rational drug dosing strategies. The optimal time for studying food-drug interactions would be at the end of the first phase I clinical trial: once the dose-toxicity relationship has been identified. At the very minimum, the appropriate prandial state(s) should be determined before undertaking pivotal trials, given the importance of such trials in drug labeling.

It should also be noted that food restriction in the first phase I clinical trial, before the characterization of food effects, is not ideal from standpoints of pharmacology and patient safety. Because a marked decrease of AUC with food is uncommon, it is probably most appropriate—in the absence of data—to begin studies of NMEs in a fed state. On the other hand, nearly 15% of recently approved NMEs showed a marked increase in bioavailability with food. Starting the first phase I trials in fed conditions will reduce the risks of severe adverse events due to inadvertent food-drug interactions.

We recognize the limitation of this retrospective analysis, particularly with regard to identifying the rationale for apparently irrational decisions given the complex nature of oncology drug development processes and decision-making. There are potential limitations in comparing drug labels of oncology and non-oncology drugs due to different potencies, indications, and targeted patients. The inability to study other factors relevant for food labeling, such as the comparison of IV of drug exposures between prandial states with differing food contents, due to the lack of such data, is another limitation of this report. Despite these limitations, our analysis clearly illustrates a distinct food labeling pattern with oncology products that is inconsistent with the fundamental principles routinely practiced in other disciplines. Although there is understandable urgency that might be unique to oncology, it is important that regulatory agencies insist on the uniform application of principles of clinical pharmacology, regardless of the effect on the sponsor’s timelines.

Table 2. Drugs with positive food effect with meals and black box safety warnings

<table>
<thead>
<tr>
<th>Drugs with positive food effects* and black box safety warnings</th>
<th>Therapeutic area</th>
<th>Black box warning</th>
<th>Risk of QT prolongation</th>
<th>AUC ratio (fed/fasted)</th>
<th>Warning regarding food effect</th>
<th>Label</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ziprasidone HCl</td>
<td>Non-oncology</td>
<td>Elderly with dementia related psychosis with increased risk of death</td>
<td>Yes</td>
<td>2</td>
<td>No</td>
<td>Fed</td>
</tr>
<tr>
<td>Lapatinib</td>
<td>Oncology</td>
<td>Hepatotoxicity</td>
<td>Yes</td>
<td>4.1</td>
<td>No</td>
<td>Fasted</td>
</tr>
<tr>
<td>Nilotinib</td>
<td>Oncology</td>
<td>QT prolongation</td>
<td>Yes</td>
<td>1.74</td>
<td>Yes</td>
<td>Fasted</td>
</tr>
</tbody>
</table>

*Positive food effect: increase of AUC by at least 25% with meals.

Disclosure of Potential Conflicts of Interest

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